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SURFACTANT SYSTEMS

Their Chemistry, Pharmacy and Biology

D. Attwood and A. T. Florence

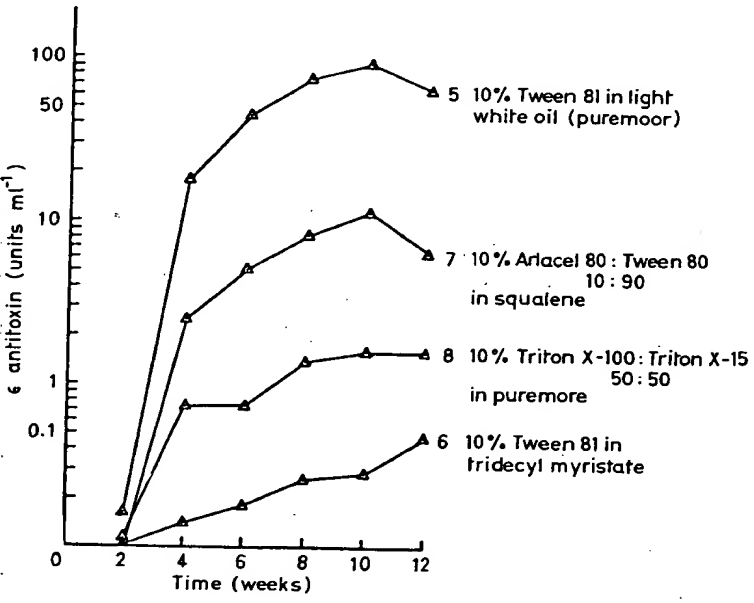


Figure 6.32 ε-Antitoxin titres in guinea-pig serum ($n = 6$) after 1 ml subcutaneous doses of vaccines 5–7 and a 0.2 ml dose of vaccine 8. From Coles *et al.* [238].

be solubilized. They also found that water was solubilized in paraffin oil and pure hydrocarbons, straight or branched, at lower concentrations in fatty alcohols and fatty acid esters and at extremely low concentrations in vegetable oils, pure triglycerides and fatty alcohol esters. This then limits non-aqueous solubilization for medicinal products. Vaccines in tridecyl myristate and squalene as well as mineral oil were examined and in one system (8) a Triton X-100/Triton X-15 mixture was used (unsuccessfully) as the solubilizer. ε-Antitoxin titres produced in rabbit serum on administration of four of these vaccine formulations are shown in Fig. 6.32. The tridecyl myristate system was unstable at 37° C with Arlacel and Tween mixtures but the solubilized systems are generally more stable than their emulsified counterparts, although not of course immune to destabilization in a biological environment. They are now more readily prepared than emulsions and have a lower viscosity.

6.4 Solubilization with block co-polymeric surfactants

So far in this chapter we have attempted to survey solubilization of pharmaceutical products by drug class. Here we diverge to discuss solubilization by a class of surfactant. For reasons of toxicity many ionic surfactants are excluded from serious contention as solubilizing agents for use in medicines. Not all non-

ionic surfactants are without blemish in this regard, as we will see in Chapter 9, and there must still be scope for the investigation of new surfactants which can be used with impunity.

An interesting class of non-ionic surface-active agents are polyoxyethylene–polyoxypropylene–polyoxyethylene block co-polymeric surfactants, sold under the trade name Pluronic and also known by their generic name as poloxamers [239]. Of the available block co-polymeric surfactants, the poloxamers have been most widely studied to date, yet there has been considerable confusion in the literature over the exact nature of their colloidal behaviour, in particular whether or not micelles are formed [240]. Recently, surface-tension measurements on a series of poloxamers in aqueous solution [241] and photon correlation spectroscopy [242] has helped to resolve some of these problems but as befits their structure their behaviour patterns tend to be complex. At low concentrations, approximating to those at which more conventional non-ionic detergents form micelles, the poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentrations these monomolecular micelles associate to form aggregates of varying size which have the ability to solubilize drugs [243] and to increase the stability of solubilized agents [244].

Table 6.27 lists approximate values of molecular weight and ethylene oxide and propylene oxide chain lengths for the poloxamers, and the designation of poloxamers and the commercial Pluronic surfactants.

Table 6.27 Approximate values of n, m and M for various polyoxyethylene–polyoxypropylene glycols (Pluronic or poloxamers)

Poloxamer designation	Pluronic* designation	Molecular weight of C_3H_6O- portion	m†	'Percent' C_2H_4O	Molecular weight of C_2H_4O- portion	n†	Total molecular weight, M
181	L61	1 750	23	10	194	4	1 944
182	L62	1 750	23	20	438	10	2 188
183	L63	1 750	23	30	750	17	2 500
184	L64	1 750	23	40	1 167	27	2 917
185	P65	1 750	23	50	1 750	40	3 500
188	F68	1 750	23	80	7 000	159	8 750
231	L81	2 250	30	10	250	6	2 500
234	P84	2 250	30	40	1 500	34	3 750
235	P85	2 250	30	50	2 250	51	4 500
237	F87	2 250	30	70	5 250	119	7 500
238	F88	2 250	30	80	9 000	205	11 250
331	L101	3 250	43	10	361	8	3 611
333	P103	3 250	43	30	1 393	32	4 643
335	P105	3 250	43	50	3 250	74	6 500
338	F108	3 250	43	80	13 000	296	16 250
101	L31	950	13	10	106	2	1 056
401	L121	4 000	53	10	444	10	4 444

* F denotes 'solid', P denotes 'pasty' and L denotes 'liquid' consistencies at 25°C.
† Molecular weight of C_3H_6O– is 76 and of C_2H_4O– is 44.

Some relationships between poloxamer structure and the solubilization of para-substituted acetanilides have been defined by Collett and Tobin [243]. The solubilities of the substituted acetanilides such as 4-hydroxyacetanilide, in aqueous poloxamer solutions increase with increasing oxyethylene content of the polymer although the more hydrophobic members of the series do not show this trend [243]. The results as expressed in Table 6.27 show that, for example, 4-nitroacetanilide is less soluble in the more hydrophilic poloxamers, and this is the general trend shown by the halogenated derivatives. These are apparently contradictory results. Some attempt was made to relate solubilization of the series to the π values of their functional groups. Thus in Table 6.28 we see solubilization expressed as the slope of the plot of mol drug solubilized mol^{-1} poloxamer against percentage ethylene oxide in the surfactant. Slope of the hydrophilic derivatives are thus positive and those of the more hydrophobic compounds, negative. A linear relationship is obtained for the solubilization of a hydrophobic acetanilide, 4-fluoroacetanilide and the propylene oxide–polyethylene oxide ratio of the solubilizer (Fig. 6.33a) but when the amount of drug solubilized by the hydrophobe is calculated it decreases as the hydrophobicity of the solubilizate increases, which is contrary to expectation (Fig. 6.33b). Collett and Tobin suggest some hydrophobic barrier in the micelle which seems unlikely, but there is no doubt that the micellar properties are not as predicted [241]. Apparent critical micelle concentrations determined from surface tension measurements decrease with increasing HLB. The fact that this is contrary to expectation might lead one to suspect that these are not true CMCs but are the consequence of interaction between the solubilizate and polymer. Methyl, ethyl, and propyl parahydroxybenzoate, for example, interact with poloxamer co-polymers to no greater extent than they do with polyoxyethylene glycol 6000 which does not micellize; butyl parahydroxybenzoate, on the other hand, is solubilized to a greater extent in this Pluronic than by polysorbate 80. The flexibility of the chains at the air–water

Table 6.28 The slopes for plots of mol *p*-substituted acetanilide solubilized mol^{-1} poloxamer (pH 1.0, 37° C) against percentage oxyethylene in the poloxamer molecule and the π value of the substituent (from [247])

Substituent	Slope, $K \times 10^2$	π*
H	6.30	0
4-OH	15.0	−0.36
4-OMe	2.74	−0.133
4-OEt	0.31	0.367†
4-CHO	5.20	0.091
4-NO_2	−0.32	0.499
4-F	−1.30	0.309
4-Cl	−0.78	0.714
4-Br	−1.03	1.130
4-I	−0.83	1.303

* From [245]
† From [246].

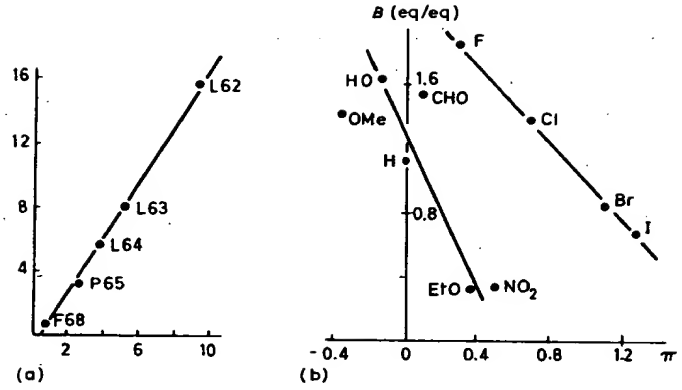


Figure 6.33(a) Solubilization of 4-fluoroacetanilide in aqueous solutions of poloxamers L62, L63, L64, P65 and F68 expressed as equivalents of drug per equivalent of ethylene oxide against the poloxamer mole ratio. Ordinate: $S/C_{EO} \times 10^2$ (equivalents of drug solubilized per equivalent of ethylene oxide). Abscissa: $C_R/C_{EO} \times 10^2$ (propylene oxide–ethylene oxide mol ratio). (b) The amount of *p*-substituted acetanilide solubilized (B) by the hydrophobe of poloxamer molecules as a function of the π value of the substituent group on the acetanilide molecule. From Collett and Tobin [247].

interface [241] suggests that the folding of the longer hydrophobic chains in bulk solution effectively decreases the exposed hydrophobic surface and this reduces the tendency to form polymolecular aggregates even though the monomer is calculated to be more hydrophobic through its HLB number. Another explanation of the trends may be that when the polyoxyethylene chains are short the molecules do not display sufficient amphipathy. Amphipathic properties increase with increase in the size of the hydrophile. Some evidence for this is that the addition of sodium chloride to a solution of poloxamer L64 causes a reduction in the measured mean radius of the aggregates in solution, suggesting that salting out of the hydrophile at both ends of the molecule converts it into a non-aggregating species, by making it more closely resemble a hydrocarbon chain [241].

Nuclear magnetic resonance has been used [248] to study the interaction of poloxamer F68 and phenol. Starting with low phenol concentrations, up to 2%, in a 10% aqueous poloxamer F68 solution, it was reported that the phenol was associated mainly with the polyoxypropylene chain. However, as the ratio of phenol to poloxamer increased, it appeared that the polyoxypropylene chain became saturated with phenol and relatively more phenol entered the polyoxyethylene chain.

A chlorhexidine gluconate–poloxamer 187 solution has been developed as an antiseptic skin cleansing formulation [249]. This contains 25% poloxamer 187, chosen to produce the greatest foaming capacity and also because the poloxamers as a class interfere with the activity of the chlorhexidine less than other non-

ionic surfactants tested.
Choice of poloxamer re
and its ability to solubi

Marked increases in
achieved by dispersing
carrier [251] (see Fig. 6.
in the digoxin co-precip
shown in Table 6.29 in w

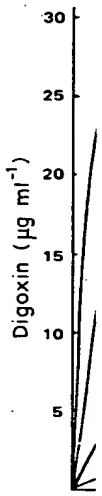


Figure 6.34 Dissolution o
drug; △, 10 and 1% physic
From Neddy *et al.* [251]

Table 6.29 E
solubility of

Test system
Water
Poloxamer 18
equivalent t
Poloxamer 18
equivalent t
Deoxycholic a
equivalent t
Deoxycholic a
equivalent t

From [251].

ionic surfactants tested. An alcohol-based mouthwash has also been described. Choice of poloxamer rested on lack of noxious taste (cf. some other non-ionics) and its ability to solubilize aromatic flavours [250].

Marked increases in the dissolution rate of digitoxin and digoxin has been achieved by dispersing the drugs in solid poloxamer 188 (Pluronic F68) as a carrier [251] (see Fig. 6.34). Poloxamer 188, in concentrations equivalent to that in the digoxin co-precipitates studied, increased the solubility of the digoxin as shown in Table 6.29 in which results are compared with the effects of deoxycholic

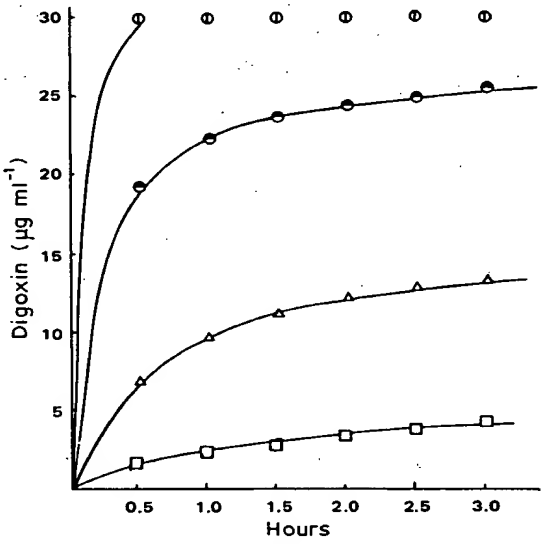


Figure 6.34 Dissolution of digoxin from poloxamer 188 test preparations. □, Untreated drug; △, 10 and 1% physical mixtures; ◓, 10% co-precipitate; and Φ, 1% co-precipitate. From Neddy *et al.* [251] with permission.

Table 6.29 Effect of poloxamer 188 and deoxycholic acid on the solubility of digoxin in water at 37° C

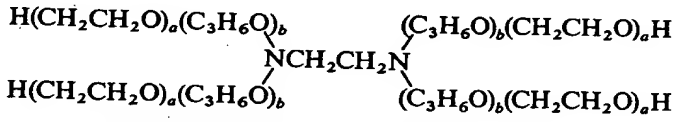
Test system	Solubility mg/100 ml
Water	3.47
Poloxamer 188 in concentration equivalent to 10% co-precipitate	4.77
Poloxamer 188 in concentration equivalent to 1% co-precipitate	5.38
Deoxycholic acid in concentration equivalent to 10% co-precipitate	4.62
Deoxycholic acid in concentration equivalent to 1% co-precipitate	4.25

From [251].

acid. Enhanced dissolution could be due to the presence of the drug in an amorphous state in the co-precipitate, to surface-tension lowering and to increase in the bulk solubility of the dry substance (see Chapter 7).

Poloxamers have also been incorporated into white petrolatum USP ointment bases in the presence of dimethylsulphoxide to modify the absorption of drugs presented in the base [252]. Percutaneous absorption of salicylic acid was increased significantly by poloxamers 231 and 182 and absorption of sodium salicylate by poloxamer 182.

Sheth and Parrott [244], in their study on the hydrolysis of esters, measured the solubility of benzocaine in a range of non-ionic surfactants including poloxamer 188. It was the least efficient, a Tetronic co-polymeric surfactant (Tetronic 908) having twice the solubilizing capacity. Tetronic is the proprietary name for the poloxamine series with the general structure,



(XXIV) Poloxamine (Tetronic) structure

Table 6.30 Nomenclature of the meroxapol and poloxamine block co-polymeric surfactants

Meroxapol series

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
3100	31R1	31R2	—	31R4	—	—	—	—
2500	25R1	25R2	—	25R4	25R5	—	—	25R8
1700	17R1	17R2	—	17R4	—	—	—	17R8
1000	—	—	—	—	10R5	—	—	10R8

% Ethylene oxide

Poloxamine series

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
6750	1501	1502	—	1504	—	—	—	1508
5750	1301	1302	—	1304	—	—	1307	—
4750	1101	1102	—	1104	—	—	1107	—
3750	901	—	—	904	—	—	—	908
2750	701	702	—	704	—	—	707	—
1750	—	—	—	504	—	—	—	—
750	—	—	—	304	—	—	—	—

% Ethylene oxide

From Schmolka [239].

The nomenclature of the poloxamers and the meroxapols (polyoxypropylene–polyoxyethylene–polyoxypropylene block co-polymers) 'reversed' poloxamers is explained in Table 6.30. Another class of block co-polymers which has no generic name has the name Pluradot (Wyandotte). These have three block co-polymer chains with the general formula,

$$R[O(C_3H_6O/CH_2CH_2O)_n-(CH_2CH_2O/C_3H_6O)_mH]_3$$

$$\left(\frac{C_3H_6O}{C_2H_4O}\right)>1 \qquad \left(\frac{C_2H_4O}{C_3H_6O}\right)>1$$

Pluradot structure
XXV

The solubilizing ability of these complex polymers has not been reported.

6.5 Polymer–surfactant interactions

Pharmaceutical formulations are rarely simple solutions. The increasing likelihood of the presence of polymers in formulations should alert us to the possibility of surfactant–polymer interactions which can influence the capacity of the surfactants to perform their function of increasing the solubility of drug substance. Polymer–surfactant interactions are of some interest in view of the use of polymers as viscosity modifiers and suspension stabilizers [253]. Interactions between surfactants and non-ionic polymers such as polyethylene oxides [254], polypropylene oxides [255], polyvinylpyrrolidone [256, 257] and polyvinylalcohol [260] have been studied [259]. An interesting property of some of these polymer–surfactant complexes, e.g. polyvinylpyrrolidone–NaLS, is the synergistic effect of the polymer on the capacity of the surfactant to solubilize oil-soluble dye [256, 257]. An instance of such synergism occurring in hydrocarbon media has also been reported [260]. Interactions between polymer and a given surfactant increase with the increasing hydrophobicity of the macromolecule; indeed it has proved possible to solubilize poorly soluble hydrophobic polymers by the addition of surfactant [261, 262]. Polyelectrolytes form precipitation complexes with oppositely charged surfactants which can in many cases be completely re-solubilized by the addition of excess surfactant [259]. Maximum precipitation has been found to occur when a single layer of adsorbed surfactant formed on the polymer chains; the resolubilized form appearing when a double layer of surfactant was achieved. Goddard and Hannan's detailed study [259] has revealed that optimal interactions between polymer and surfactant occurred when the surfactant had a long, straight hydrocarbon chain with the polar group terminal to the alkyl chain. Departure from this structural constraint reduces the extent of the interaction and also renders the resolubilization difficult, the latter being difficult to achieve if the charge density on the polymer is also high [259]. As might be expected, the complex formed between some surfactants and polymers has a solubilization capacity which is different from that of the surfactant alone. Fig. 6.35 shows the effect of PVP on the solubilization of Yellow

The Condensed Chemical Dictionary

EIGHTH EDITION

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mers of styrene/butadiene, acrylonitrile/butadiene and others.

"Pliovic" Latices.[265] Trademark for vinyl polymer and copolymer latices.
300 Series. Straight vinyl chloride latices especially suited for paper and textile coatings, rug and carpet backings, nonwoven fabrics.
400 Series. Vinyl chloride/acrylate copolymer latices which form hard, tough thermoplastic films at room temperature. Useful in exterior wood and masonry paint, paper and textile coatings, nonwoven fabrics.

"Pliovic" Vinyl Resins.[265] Trademark for a group of thermoplastic resins composed of polymers and copolymers consisting of 50% or more vinyl chloride. Supplied in the form of fine white powders, the resins are easily compounded and formed into finished goods by extruding, calendering, compression molding, injection molding and blow molding.

plumbago. See graphite.

plumbic acid, anhydrous. See lead dioxide.

plumbo-plumbic oxide. See lead oxide, red.

"Plumb-O-Sil" B and C.[304] Trademark for coprecipitates of lead orthosilicate and silica gel.
Properties: Soft white powders; sp. gr. (B) 3.9, (C) 3.1; refractive index, (B) 1.58-1.60, (C) 1.58.
Containers: Up to 150-lb. fiberboard drums.
Uses: Translucent and colored vinyl film, sheeting, and upholstery stocks; as vinyl stabilizers.

plumbous oxide. See litharge.

plumbous sulfide. See lead sulfide.

plumbum. The Latin name for lead, hence the symbol Pb and the names plumbic and plumbous.

"Pluracol."[203] Trademark for a series of organic compounds used in hydraulic brake and other functional fluids; chemical intermediates; urethane foams, elastomers and coatings.

"Plurafac."[203] Trademark for a series of 100% active, nonionic biodegradable surfactants of straight chain, primary aliphatic, oxyethylated alcohols designed through advanced synthesis techniques. Available in liquid, paste, flake, and solid form.
Uses: Range from light-duty hand dishwashing formulations to heavy-duty industrial detergents, rinse aids, metal cleaners, etc.

"Pluronic."[203] Trademark for a nonionic series of 28 related difunctional block-polymers terminating in primary hydroxyl groups with molecular weights ranging from 1,000 to over 15,000. They are polyoxyalkylene derivatives of propylene glycol. Available in liquid, paste, flake, powder and cast-solid forms.
Uses: Defoaming agents, emulsifying and demulsifying agents, binders, stabilizers, dispersing agents, wetting agents, rinse aids, and chemical intermediates.

"Plus Fifty B."[548] Trademark for a formulation composed primarily of sodium bicarbonate. Used to extinguish fires in flammable liquids (Class B fires).

"Plus Fifty C."[548] Trademark for sodium bicarbonate formulation; used to extinguish flammable liquid fires.

plutonium Pu Synthetic radioactive metallic element with atomic number 94; first prepared in 1941 as the 238 isotope by bombarding uranium with deuterons. Atomic weight 239.11. Valences 3, 4, 5, 6. Fifteen isotopes (from 232 to 246); six allotropic forms. Plutonium 239 (half-life 24,360 years) is of major importance since it is fissionable by both high- and low-energy neutrons. It is produced by bombarding uranium 238 with slow neutrons in a nuclear reactor. Used as a nuclear reactor fuel and for nuclear weapons. Can be recovered from spent fuel by solvent extraction with tributyl phosphate diluted with kerosine. Plutonium exists in nature in uranium-containing ores in concentrations of a few parts per trillion. Plutonium is similar chemically to uranium and neptunium, forming analogous compounds such as PuO_2, PuF_3, PuF_4, PuOCl, etc. M.p. 641°C; b.p. 3327°C. Highly fissionable.
Hazard: Highly toxic radioactive poison. Must be handled by remote control and with adequate shielding. For safety details, consult Atomic Energy Commission, Washington, D.C.

plutonium 242. An isotope of plutonium now available from AEC.
Hazard: Radioactive poison.
Uses: Tracer techniques; analytical chemistry.

"Plyac."[50] Trademark for polyethylene spreader-sticker; nonoily and nonionic.

"Plyacien."[36] Trademark for a protein base dust-free adhesive for use with the cold press no-clamp gluing process.
Use: Manufacture of interior grade plywood.

"Plyamine."[36] Trademark for a group of liquid water-soluble urea-formaldehyde adhesive resins used as binders in the manufacture of plywood, furniture, wood particle products, etc.

"Plyamul."[36] Trademark for polyvinyl acetate adhesive bases.

"Plyophen."[36] Trademark for a water-soluble impregnating resin. Penetrates deeply and quickly into wood, canvas, asbestos, paper and other laminating and molding stocks. Can be diluted as much as 8-10 parts water to 1 part resin for spraying glass fiber or rock wool.

plywood. A composite composed of thin wood veneers (with grains placed at right angles to each other) bonded with a synthetic resin, usually phenol-formaldehyde or resorcinol-formaldehyde. It is superior to metals in strength-to-weight ratio, and has low thermal expansion, high heat capacity, and low water absorption. See also laminate; composite.

Pm Symbol for promethium.

PMA. Abbreviation for phosphomolybdic acid and for pyromellitic acid.

"PMA."[74] Trademark for a series of fungicides containing phenyl mercury acetate. Used in emulsion paint and other aqueous systems.
Hazard: See mercury compounds.

"PMAS."[49] Trademark for a colorless, odorless, stable water solution containing phenylmercury derivatives; used as a fungicide, germicide and herbicide.
Hazard: See mercury compounds.

"PMD-10."[74] Trademark for a mineral spirits solution of phenyl mercury oleate. Used for mildew-resistant oil, oleoresinous and alkyd paints.
Hazard: See mercury compounds.

PMDA. Abbreviation for pyromellitic dianhydride (q.v.).

PMHP. Abbreviation for para-menthane hydroperoxide. A polymerization catalyst.

PMP. Abbreviation for 1-qhenyl-3-methyl-5-pyrazolone (q.v).

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Physical Chemistry

PLURONIC® surfactants, unlike conventional nonionic surfactants, do not micellize at a critical micelle concentration (CMC). Instead, aggregation occurs over a broad concentration range that we refer to as the ACR (aggregation concentration range). The limiting aggregation concentration (LAC) is the point at which the surfactant reaches saturation, which would correspond to the more conventional CMC. The ACRs and LACs for these surfactants occur at much higher orders of magnitude (for most of the products >1000 ppm) than for classical nonionic surfactants (commonly below 100 ppm) with a single hydrophile and a single hydrophobe, as shown below.

PLURONIC® Surfactants

Product	Aggregation Concentration	Limiting Aggregation

	Range (ppm)	Concentration (ppm)
L35	2,000-100,000	>100,000
P65	200-50,000	>50,000
P75	1,000-50,000	>50,000
P85	500-50,000	>50,000
P103	50-1,000	>1,000
P104	100-1,500	>1,500
P105	50-2,000	>2,000
F108	400-50,000	>50,000

Many of the unique performance benefits provided by PLURONIC surfactants and highlighted throughout this site can be explained on a molecular level by the unusual aggregation behavior observed with these products.

BASF Corporation has many years of expertise in research process development, production and application of EO/PO block copolymer surfactants.

These BASF surfactants range from flowable liquids of varying viscosities to pastes, prills and cast solids, with molecular weights from 1,000 to 30,000. All products are 100% active and all are easy to handle, physically stable and have an extremely low order of oral and dermal toxicity.

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